REMARKS

Entry of the present amendment is respectfully requested. Claim 1 has been canceled. New claims 105-120 have been added. No new matter has been added.

Rejection of claim 1 under 35 U.S.C. 112, first paragraph

Claim 1 was rejected under 35 U.S.C. 112, first paragraph for lack of an enabling disclosure. The Office Action asserts that although the specification of the instant application is enabling for a method for delivering a nucleic acid into a cell, the specification allegedly does not provide enablement for delivering any compound into a cell by administration of the compound with any organic halide. This rejection is respectfully traversed.

Claim 1 has been canceled and replaced by new claim 105. The specification is enabling for administering to a cell a composition comprising a compound to be delivered and an organic halide and applying ultrasound to the cell as recited in new claim 105.

Nature of the Invention/Breadth of Claims

The Office Action asserts that the claims encompass "a very large genus of structurally and functionally divergent molecules." Office Action dated August 24, 2004, page 6. The Office Action further asserts that "the compound of the claims is of essentially unlimited scope" (page 6). Thus, the Office Action concludes that although the specification enables delivering a nucleic acid into a cell (Office Action, page 7), the specification fails to enable delivering compounds other than nucleic acid molecules.

New claims 105-120 recite delivering a compound and an organic halide to a cell. The specification further discloses exemplary compounds and organic halides for delivery to a cell. *See, e.g.*, specification at page 42-45 (compounds) and Table 1 (organic halides). Viewed as a whole in combination with other factors as set forth below, one of skill in the art would be enabled to practice the claimed invention without undue experimentation.

State of the Prior Art/Predictability in the Art

The Office Action cites various passages from Godbey, *J. Control. Release* 72: 115-125 to conclude that "critical parameters that enable ... gene delivery vehicles ... are not well understood and ... even small changes in the structure of a molecule can have dramatic effects on its functional properties." See Office Action, page 7. Based on this assertion, the Office Action concludes that "the art provides no ... guidance as to which organic halides would be operative in the method." Office Action, page 7.

Godbey discloses that "not all gene delivery vehicles operate in the same fashion." Godbey, page 119, col. 2. However, Godbey does not address the use of organic halides for delivering compounds into a cell. Godbey does not disclose that the use of different organic halides is unpredictable. Rather, Godbey merely discloses that the use of different classes of agents may result in differences in transfection efficiencies. Moreover, Godbey states that "[t]his does not mean that what is shown for one gene transfer methodology is not applicable to others; one should merely be aware that there is not a single explanation of cellular processing that covers all non-viral gene delivery vehicles." Although Godbey might suggest that there is no single explanation to explain the potential differences in the mechanism of transfection, Godbey

does not suggest that use of different organic halides would be unpredictable. Godbey does not disclose the use of organic halides at all.

The Office Action further asserts that "... delivery of many compounds across cell walls and membranes has proved more difficult than for ... nucleic acid ..." See Office Action, page 8. In support of this assumption the Office Action cites Hawiger and Veach. However, Hawiger discloses a method of noninvasive intracellular delivery of peptides and proteins, *i.e.*, a "means for easy and rapid delivery of peptides and proteins to a wide spectrum of cells." See Hawiger, abstract. Thus, rather than demonstrating the "unpredictability" of intracellular delivery of peptides and proteins as the Office Action contends, Hawiger teaches the feasibility of intracellular delivery of peptides and proteins.

The Office Action cites Hawiger as disclosing that "[t]he plasma membrane of eukaryotic cells is inherently impermeable to peptides and proteins that lack specialized membrane receptors or transport proteins". However, this statement fails to demonstrate the unpredictability of organic halides in delivering a compound into a cell. Rather, Hawiger merely discloses a characteristic of the plasma membrane of a eukaryotic cell (namely, impermeability to proteins). In fact, Hawiger discloses an alternate (apparently successful) method of intracellular delivery of peptides into a cell thus demonstrating the predictability of intracellular delivery of peptide/proteins. Hawiger does not suggest that the use of organic halides would be unpredictable in delivering compounds into a cell. Hawiger does not disclose the use of organic halides at all.

The Office action also cites Veach as suggesting that "the mechanism by which ... peptides translocate cargo across the plasma membrane remained unexplained." See Office

Action, page 8. The Office Action combines the disclosures of Veach and Hawiger to assert that "development of methods to introduce a very large class of compounds (*i.e.*, peptides and proteins) into a cell was at a very early stage of development." Office Action, page 8. However, as stated above, Hawiger discloses a successful method of intracellular delivery of proteins. Veach merely suggests that the mechanism of translocation is "unexplained." Even if details of the mechanism of how translocation is accomplished are still "unexplained," there is no suggestion that translocation would not be successful or that translocation would be unpredictable. Unexplained results does not imply unpredictability – only that a clear reason for the success of the method is not yet known. Furthermore, Veach does not teach or suggest that the use of organic halides in delivering a compound into a cell is unpredictable. Veach does not disclose the use of organic halides at all.

Amount of Direction Provided by the Inventor/Existence of Working Examples

The Office Action correctly states that the specification need not contain a working example to be enabling (see Office Action, page 9) but concludes that the lack of a working example in combination with the prior art teachings (*i.e.*, Godbey, Hawiger and/or Veach) renders the instant specification non-enabling.

The Office Action acknowledges that the instant specification (*e.g.*, Table 1) discloses embodiments of the claimed invention with specific organic halides but asserts that there is "no evidence" in the specification that "any of these embodiments would ... deliver any compound across the plasma membrane ... in the absence of a lipid carrier or ultrasound." New claim 105

recites applying ultrasound to the cell sufficient to induce uptake of the composition into the cell. Therefore, the method of new claim 105 includes ultrasound.

The Office Action further asserts that there is "no evidence ... to indicate that any compound other than a nucleic acid could be delivered into a cell." See Office Action, page 10. However, the specification explicitly discloses delivering compounds into a cell including compounds listed in the specification at pages 42-45. Contrary to the Office Action's assertions, the specification provides a teaching of compounds other than a nucleic acid that can be delivered into a cell.

The Office Action further asserts that prior art teachings "suggest that only a small fraction ... of the organic halides of the claims would be capable of facilitating transport of a compound across the plasma membrane in the absence of a lipid carrier or ultrasound." This contention is inaccurate for at least the following reasons. First, the prior art cited in the Office Action (*i.e.*, Godbey, Hawiger and Veach) generally discloses the successful noninvasive intracellular delivery of proteins (Hawiger), successful, facile delivery of biologically active peptides (Veach, abstract) and mere differences in efficiencies in the use of different classes of compounds for gene delivery in a cell (Godbey). Thus, rather than suggesting the unpredictability of delivering compounds into a cell, the cited references suggest that delivering compounds into a cell is not only predictable but has been accomplished in the art (albeit using different methods). Notably, none of the cited references suggest that only a small fraction of organic halides is capable of facilitating transport of a compound across a plasma membrane as the Office Action contends. As noted above, the cited prior art references do not disclose organic halides at all much less what fraction of organic halides deliver compounds into cells. Secondly,

even if Godbey, Hawiger and/or Veach did disclose organic halides, the instant claims do not recite transporting compounds across plasma membranes in the absence of ultrasound.

Relative Skill in the Art/Quantity of Experimentation to Make or Use

The Office Action concedes that the level of skill in the art is high (Office Action, page 10) but nevertheless concludes that one of skill in the art (despite the high level of skill in the art) would still be unable to practice the claimed invention without undue experimentation based on the assumption that there must be a large number of "inoperative embodiments." The Office Action does not identify any specific embodiment in the instant specification as being inoperative but rather merely assumes that there must be many.

As noted above, the prior art references cited (Godbey, Hawiger and Veach) do not disclose the use of organic halides. Nor do any of the prior art references teach or suggest that the use of organic halides would be unpredictable or inoperative. Godbey discloses a potential difference in efficiencies of delivery (not inoperativeness) but provides no comments on organic halides. Hawiger discloses a successful method of noninvasive intracellular delivery of peptides and proteins but provides no comments on organic halides. Veach discloses facile delivery of peptides in cells but likewise does not disclose that use of any organic halides would be inoperative. Without a showing that any of the embodiments might be inoperative, the Office Action has failed to establish inoperability of *any* of the embodiments disclosed in the instant specification. Furthermore, even assuming *arguendo* that an embodiment were inoperative, as the Office Action correctly points out, "the presence of inoperative embodiments within the

scope of a claim does not necessarily render a claim nonenabled." See Office Action, page 11, quoting *Atlas Powder Co. V. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414.

New claim 119 is similar to claim 105 and is allowable for at least the reasons set forth above for claim 105. New claims 112-118 depend from claim 105 and new claim 120 depends from claim 119. Therefore, claims 112-118 and 120 are allowable for at least the reasons set forth above.

New claim 106 recites that the compound is an exogenous nucleic acid sequence. The Office Action concedes that the specification is enabling for delivering a nucleic acid into a cell comprising administering a composition comprising a nucleic acid and an organic halide. Therefore, 106 and dependent claim 107 are allowable.

Rejection of claim 1 under 35 U.S.C. 102(b) over Unger (WO 94/28780)

Claim 1 was rejected under 35 U.S.C. 102(b) as being anticipated by Unger (WO 94/28780). Claim 1 has been cancelled. This rejection is rendered moot in view of cancellation of claim 1. New claim 105 and new dependent claims 106-118 recite a composition comprising a compound to be delivered to a cell and an organic halide to form a mixture, wherein the mixture does not comprise a liposome. WO 94/28780 discloses a composition delivered to a cell, the composition comprising liposomes. New claim 119 and dependent claim 120 recite applying ultrasound to the cell at 200-500 milliwatts per cm^2. WO 94/28780 fails to teach or suggest applying ultrasound to a cell at 200-500 milliwatts per cm^2.

Rejection of claim 1 under 35 U.S.C. 102(b) over Kabanov (US Patent No. 5,656,611)

Claim 1 was rejected under 35 U.S.C. 102(e) as being anticipated by Kabanov et al. This rejection is respectfully traversed.

Claim 1 has been canceled. New claims 105-120 recite applying ultrasound to the cell. Kabanov does not disclose applying ultrasound.

Rejection of claim 1 under 35 U.S.C. 102(b) over Eppstein (US Patent No. 5,550,289)

Claim 1 was rejected under 35 U.S.C. 102(e) as being anticipated by Eppstein et al. This rejection is respectfully traversed.

Claim 1 has been canceled. New claims 105-120 recite applying ultrasound to the cell. Eppstein does not disclose applying ultrasound.

Rejection of claim 1 under 35 U.S.C. 103(a) over US Pat. Nos 5,830,430; 6,056,938; and 5,997,898

Claim 1 was rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. Nos. 5,830,430; 6,056,938; and 5,997,898. This rejection is rendered moot in view of cancellation of claim 1.

Rejection of claim 1 under obviousness-type double patenting

Claim 1 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No 6,638,767, claims 1-35 of U.S. Patent No. 6,743,779, claim 125 of U.S. Patent No. 5,830,430, claims 73-81 of U.S. Patent No.

6,056,938, and claim 12 of U.S. Patent No. 5,997,898. Applicants will consider the filing of a terminal disclaimer upon notification of allowable subject matter.

In view of the above amendments and remarks, Applicants respectfully submit that the instant application is in condition for allowance. If the Examiner feels, however, that further amendment and/or discussion may be helpful in facilitating prosecution of the case, the Examiner is respectfully requested to telephone the undersigned attorney of record at the number appearing below.

Respectfully submitted,

FOR Sarah A. Kagan
Registration No. 32,141

BANNER & WITCOFF, LTD.
1001 G Street, N.W.
11th Floor
Washington, D.C. 2001
(202) 824-3000
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